that the only cited utilities of the protein encompassed by the present claims that are provided in the specification are to detect the protein, to make antibodies, and to screen drugs, and that while these utilities are credible, they are allegedly neither specific nor substantial (pages 2-5). In addition, the Examiner addresses Applicants' response of February 28, 2002 on pages 8-12 of the June 6, 2002 Office Action and states that the Applicants' arguments are not persuasive.

Regarding substantial utility, the Examiner states that the protein of invention lacks substantial utility because: 1) while it is encoded by a gene found in a genetic region associated with schizophrenia, it is allegedly not associated with schizophrenia; 2) while it is expressed in the brain, many other nonpathogenic proteins are expressed in the brain; and 3) while proteins with glutamine repeats are linked to neurological disease, glutamine repeats are not limited to proteins associated with neurological disorders.

Applicants respectfully submit that the Examiner has set an improper standard for substantial utility. Applicants have presented an overwhelming preponderance of evidence that the protein of the invention,G713, possesses substantial utility. G713 is encoded by a gene in chromosomal region 13q31-33. According to data available on the NCBI website, there are only 167 genes in this region (see included reference). Furthermore, Applicants acknowledge that glutamine repeats may not be *limited* to proteins associated with neurological disorders, only that there is enormous precedence for the presence of glutamine repeats in such proteins (see, for example, Margolis, *et al.*, *Human Genetics* (1997) 100:114-122). However, the average skilled practitioner, when presented with the fact that the protein of the invention: 1) is encoded by one of 167 genes in a genomic region strongly associated with schizophrenia; 2) is expressed specifically in the brain; 3) as pointed out by the Examiner, is one of only 310 human sequences with at least nine CAG repeating units; and

4) contains glutamine repeats, which are present in a number of proteins associated with neurological disorders, would undoubtedly find that the protein of the invention has substantial utility as a diagnostic tool. The Utility guideline for substantial utility (page 6) reads, "An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a 'real world' context of use in identifying potential candidates for preventive measures or further monitoring." Determining predisposition to schizophrenia in an individual is clearly a substantial utility. Moreover, the data presented in the present specification sufficiently states the correlation of the claimed polypeptide with schizophrenia.

The Examiner states that the protein of the invention lacks specific utility. In support of this argument, the Examiner cites Kashima, *et al.* as evidence that the glutamine repeats present in the murine form of IL-2 allegedly do not play a role in its function. The Examiner also cites Perutz, *et al.* as evidence that glutamine repeats alone are not specific to neurodegenerative diseases.

Applicants reiterate the assertion that the protein of the invention, G713, does have a specific utility. In addition, Applicants again respectfully dispute the relevance of the Kashima paper. This reference merely demonstrates that a murine protein is unable to effect human cells, with or without the glutamine repeat region. Variability in function between species homologs is not surprising or unprecedented, as there may not be a high level of sequence conservation. For example, using the NCBI BLAST site to compare the human and murine forms of IL-2 (SwissProt accession numbers P01585 and P04351, respectively), one finds only 46% identity between the two proteins, with the best conservation limited to a span of 18 amino acids (out of 153 and 169, respectively) with 68% identity. Thus, it is not surprising that the glutamine repeats do not play a role in the function of *murine* IL-2 on human cells, as there are many *other* differences between the two proteins. Thus, the

Kashima paper is not definitive evidence that glutamine repeats do not effect function, especially the function of proteins involved in neurological disorders, and especially in light of the consensus in the literature that glutamine repeats do have a functional effect.

Applicants acknowledge that glutamine repeats may not be limited to proteins associated with neurodegenerative disorders, as allegedly demonstrated by Perutz, *et al.* It is clearly reasonable to a skilled practitioner that the presence of a stretch of charged amino acids would affect the function of any number of proteins. However, as listed in Margolis, *et al.*, pages 1-2, there is an abundance of evidence in the literature for a causitive link between glutamine repeats and neurological disease that supports the asserted utility of G713 as a diagnostic tool for a disorder such as schizophrenia.

Applicants further maintain that the utility of the G713 protein is specific. In other words, a generic protein does not possess the same properties of G713 and could not be used for the same, specific purpose of diagnosing a neuropsychiatric disorder such as schizophrenia. In particular, the genomic region encoding the present protein is strongly associated with schizophrenia, G713 is expressed mainly in the brain, and G713 is a novel member of a family of glutamine repeat-containing proteins frequently implicated in neuropsychiatric disorders. Applicants respectfully assert that the present invention meets the Utility guidelines for specificity, in that a generic polypeptide could not be used for the same purpose. In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of rejections under 35 U.S.C. § 101.

Rejection under 35 U.S.C. § 112:

In the Office Action dated June 6, 2002, the Examiner has maintained rejection of claims 58, 62, and 73-75 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which

was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. Specifically, the Examiner asserts that genetic linkage of schizophrenia is unpredictable based on a passage in Wright, *et al.* citing two recent reports that found no evidence for association of HLA with schizophrenia despite earlier studies to the contrary.

Applicants respectfully dispute the Examiner's representation of linkage studies of schizophrenia as unpredictable. The main intent of the Wright paper is to point out confounding factors that negatively affected early association studies. The recent reports referred to by Wright and the Examiner are from 1999 and point out methodological errors in studies that were carried out as long as 30 years ago. The state of the art has obviously changed since then, making genetic association more predictable and the results more reliable, as discussed further by Wright, *et al.* Early confounding factors include "small sample size, inappropriate diagnostic, laboratory, and/or statistical methodology, and/or incorrectly chosen comparison subjects" (see Wright, *et al.*, Abstract). Improvements to early methodologies are described on page 5 of Wright, *et al.* and include standardized diagnostic criteria such as DSM, technical improvements to serotyping, and introduction of genotyping to confirm or replace serotyping data. The present invention relies on advanced techniques for diagnosis, genotyping, and statistical analysis, as described in Example 2(e), page 162- Example 2(h), page 173 of the present specification. Thus, while any procedure or method based on scientific data holds some element of uncertainty, the methods used to determine the genetic association of G713 with schizophrenia are certainly as predictable and reliable as any available to the art of biotechnology. Furthermore, given the detailed disclosure, one of skill in the art would be able to use the claimed invention.

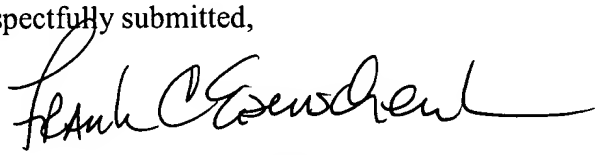
In view of the foregoing evidence, Applicants respectfully request reconsideration and withdrawal of rejections under 35 U.S.C. § 112, paragraph 1.

In view of the foregoing remarks, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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FCE/jaj

Attachment: Page from NCBI Website

Homo sapiens Map View build 30 BLAST the Human Genome

Chromosome:

1 2 3 4 5 6 7 8 9 10 11 12 [**13**] 14 15 16 17 18 19 20 21 22 X Y

Master Map: Genes On Sequence

Maps & Options

Total Genes On Chromosome: **786**

Region Displayed: **82M-108M**

bp Download/View Sequence/Evidence

Genes Labeled: **20** Total Genes in Region: **167**

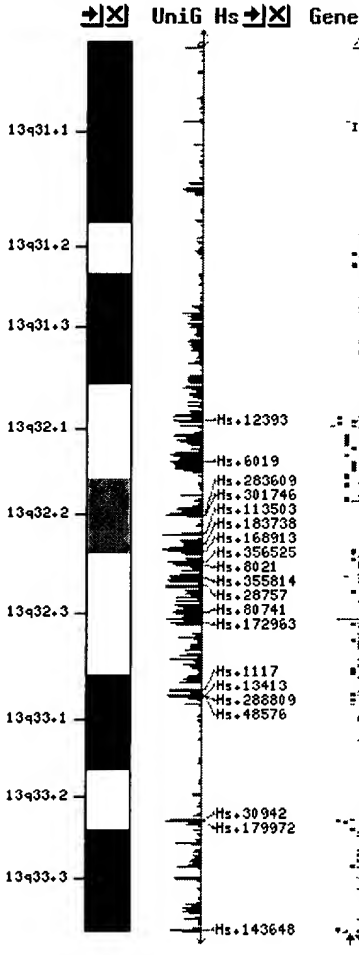
Region Shown:

13q31.1

13q33.3 Go

out zoom in

◉ ideogram
○ master



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KIAA0918	↓	sv ev hm seq mm
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TDPGD	↑	sv ev hm seq mm
CLDN10	↓	sv ev hm seq mm
GPR80	↑	sv ev - seq mm
MBLL39	↓	sv ev - seq mm
RAP2A	↓	sv ev - seq mm
KIAA1058	↑	sv ev - seq mm
LOC196540	↓	sv ev - seq mm
ZIC5	↑	sv ev hm seq mm
ZIC2	↓	sv ev hm seq mm
PCCA	↓	sv ev hm seq mm
LOC87769	↑	sv ev - seq mm
FLJ14624	↑	sv ev hm seq mm
bA430M15.1	↑	sv ev - seq mm
FGF14	↑	sv ev hm seq mm
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